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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
HADDAD, MAHER M

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 08/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/935,124	LORENS ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *7-13,17,18 and 20-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,14-16 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 6/2/03 (Paper No. 17), is acknowledged.

2. Claims 1-27 are pending.

3. Claims 7-13, 17-18 and 20-27 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

4. Claims 1-6, 14-16 and 19 are under examination as they read on a method for identifying a compound that modulates angiogenesis in vitro, wherein the compound is a small organic molecule.

5. In view of the amendment filed on 6/2/03 (Paper No. 17), only the following rejection remained.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-6, 14-16 and 19 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not reasonably provide enablement for an *in vitro* method for identifying a compound that inhibiting angiogenesis wherein the method comprises the steps of (i) contacting the compound with any ILKAP polypeptide, the polypeptide encoded by a nucleic acid that hybridizes under stringent conditions to a complement of a nucleic acid encoding a polypeptide comprising an amino acid sequence of SEQ ID NO: 2, wherein the ILKAP polypeptide has an anti-angiogenic phenotype and wherein the stringent conditions comprise a hybridization step selected from the group consisting of 50% formamide, 5X SSC, and 1% SDS, incubated at 42oC, and 5X SSC, 1% SDS, incubated at 65°C, followed by a wash step in 0.2X SSC, and 0.1%SDS at 65°C; and (ii) determining the functional effect of the compound upon the ILKAP polypeptide, whereby a difference in the functional effect as compared to the functional effect in the absence of the compound indicates that the compound modulates angiogenesis in claim 1, wherein the functional effect is a physical effect in claim 3, determined by measuring ligand binding to the polypeptide in claim 4, a chemical effect in claim 5, is determined by measuring phosphatase activity of the polypeptide in claim 6. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification does not provide a sufficient enabling description of the claimed invention. The specification discloses only a single amino acid sequence (SEQ ID NO:2) with a disclosed anti-angiogenic activity (e.g., page 45 at lines 7-9). The instant claims encompass in their breadth *any* ILCAP polypeptide encoded by a nucleic acid that hybridizes under stringent conditions to a complement of a nucleic acid encoding a polypeptide comprising an amino acid of SEQ ID NO: 2. Further, the outcome of the functional effect (either physical effect, ligand binding to the polypeptide, a chemical effect or phosphatase activity of the polypeptide) does not correlate with the end result to identify modulators of angiogenesis. There is no correlation between any functional effect, ILCAP, the compound to be screened and angiogenesis. There is insufficient guidance in the specification to assist the outcome of any functional effect and its correlation to angiogenesis, upon contacting the compound and ILCAP polypeptide of SEQ ID NO:2. One skilled in the art cannot use any functional effect as indicators of a test to determine compound's antiangiogenic potential.

The specification discloses (page 26, lines 23-31) that any suitable physical, chemical, phenotypic change that affects activity or binding can be used to assess the influence of a test compound on the polypeptide of the invention. The specification further discloses that the when the functional effects are determined using intact cells or animals, one can also measure a variety of effects such as the case of angiogenesis associated with tumors, tumor growth, neovascularization, cell surface markers such as avb3, hormone release, transcriptional changes to both known and uncharacterized genetic markers, changes in cell metabolism such as cell growth or pH changes, and changes in intracellular second messengers such as cGMP. However, none of the functional effect has not been show to correlate anti-angiogenesis phenotype with ILCAP polypeptide of SEQ ID NO:2, other than the avb3 integrin cell surface expression.

The specification discloses on page 45, lines 4-8, that ILKAP sequence was tested in relevant angiogenesis assays and demonstrated to exert a negative effect on avb3 surface expression. The specification discloses that the ILKAP-expressing endothelial cells were assayed for migration towards a ECM component. The ILKAP-expression cells were strongly inhibited in their haptotactic response, an indicator of an anti-angiogenic phenotype. While such haptotactic response is governed cell surface or extracellular matrix-associated components, applicant's method appears to require endothelial based assays to correlate such haptotactic response to angiogenesis.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Applicant's arguments, filed 6/2/03 (Paper No. 17), have been fully considered, but have not been found convincing.

Applicant argues that the elements of the claims provide adequate guidance for routine identification of the nucleic acids of the invention. Applicant argues that the functional characteristics of the proteins encoded by the claimed nucleic acids would allow one of skill in the art to identify operable embodiments and exclude inoperable embodiments. Applicant asserts that Applicants meet the PTO guidelines for enablement, which set forth the standard for the scope of enablement when a large number of possible embodiments exists.

However, the claims as written encompass a broad genus of ILCAP polypeptide with an unlimited number of possibilities with regard to the length of the polypeptide sequence. Further, polynucleotide encoding a SEQ ID NO:2 sequence does not provide that full length ILCAP protein of SEQ ID NO:2, but rather any ILCAP polypeptide. One skill in the art cannot envision all of the amino acid sequences encompassed by the breadth of the claims and having a function as anti-angiogenic.

Applicant argues that the claims recite both functional and structural characteristics of ILKAP nucleic acids of the invention. Applicant argues that the present application provides functional assays for identification of nucleic acids encoding ILKAP polypeptides of the invention without undue experimentation. Applicant concluded that one of skill, given the reference amino acid and nucleotide sequences and the specified hybridization conditions, could easily screen for other nucleic acid and protein molecules that can be used in the claimed methods.

However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the ILKCAP protein which are tolerant to change, and the nature and extent of changes that can be made in these positions. Due to the large quantity of experimentation necessary to obtain ILKAP polypeptide variants and to determine the specific activity of the infinite variants, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the state of the prior art which establishes that biological activity cannot be predicted based on structural similarity, and the breadth of the claims which embrace a broad class of structural variants, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Applicant argues that the functional assays to identify ILKAP polypeptides (i.e., with anti-angiogenic phenotypes) of the invention are known to those of skill in the art and are disclosed in the specification. Applicant asserts that the specification describes methods of determining an effect on angiogenesis through disclosure of multiple angiogenesis assays. Assays for angiogenesis include assays for expression of cell surface markers, such as $\alpha v\beta 3$, haptotaxis assays, a chick CAM assay, a mouse corneal assay and assays for neovascularization of tumors. These arguments are not commensurate with the scope of the instant claims because claim 1, recites the full scope claimed by the instant claims are any functional effect. However, there is no correlation between any functional effect, ILCAP, the compound to be screened and angiogenesis. There is insufficient guidance in the specification to assist the outcome of any

functional effect and its correlation to angiogenesis, upon contacting the compound and ILCAP polypeptide of SEQ ID NO:2. One skilled in the art cannot use any functional effect as indicators of a test to determine compound's antiangiogenic potential.

Applicant argues that one of skill in the art has only to identify nucleic acids that hybridize under specified conditions to nucleic acids that encode the conserved reference amino acid sequence of SEQ ID NO:2 using techniques described in the specification or known to those of skill in the art. Applicant contends that one of skill can readily determine, one by one, any particular ILKAP encoding nucleic acid, without undue experimentation. Applicant argues that by using nucleic acid screening, hybridization and PCR techniques, one of skill can test the functionality of the protein encoded by the nucleic acid of interest and easily determine if it falls within the scope of the claim.

While experimental testing techniques using nucleic acid screening, hybridization and PCR techniques are available, it is not routine in the art to use such methods when the expectation of success is unpredictable based on the instant disclosure. Thus, it would require an undue amount of experimentation of one skilled in the art to practice the invention as broadly claimed.

Consequently, without additional guidance in the specification, and the dearth of information in the art, for one of skill in the art to practice the invention as claimed, would require experimentation that is excessive and undue. The amount of guidance or direction needed to enable an invention is inversely related to the mount of knowledge in the state of the art as well as the predictability in the art (In re Fisher, 427 F.2d 833, 839, 166 USPQ 18,24 (CCPA 1970)).

9. No claim allowed

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
August 11, 2003

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